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Analog computer simulates heart response to nerve stimulation

Because the heart is a dynamic system whose rate changes with stimuli and time, it lends itself well to study by means of the analog computer. Experiments have been made on both the steady-state and dynamic response of the heart to vagal and sympathetic nerve stimulation

The human heart is a very complex muscle-pump system which is controlled from several different areas of the body and by many factors. Because of the experimental difficulties and the complexity of the system itself, no complete mechanical or electrical model of the system has been constructed.

This article deals with but one set of control variables—vagal and sympathetic nerve stimulation. Heretofore the study of heart response to stimulation of these two nerves has been essentially qualitative. In the test description presented here, an attempt has been made to give a quantitative analysis of this heart control system.

BIOLOGICAL REVIEW

The regular beat of the heart is self-controlled by the "pacemaker," the SA (sinuauricular) node, lying in the upper right chamber of the heart, the right auricle. From here a depolarization wave is sent through the heart muscle, causing it to contract (70 to 80 times per minute for humans, 130 to 140 times per minute for dogs). The heart rate is also controlled by other factors but it is primarily controlled by signals coming directly from the brain through the vagus and sympathetic nerves. There are four nerve bundles, the left and right sympathetic and the left and right vagus. Fibers from both sympathetic nerves and the right vagus nerve terminate in the close proximity of the SA node, while fibers of the left vagus terminate at both the SA node and the AV (auriculoventricular) node. Very little is known about the AV node except that it is possible to produce a "block" in this node and thereby stop electrical conduction from the SA node to the lower chambers of the heart, the ventricles. The connection of these nerves to the nodes is not direct, but is made by means of chemicals secreted from the nerve endings. The secretion of adrenalin from the sympathetic nerves causes an increase in heart rate, while the secretion of acethylcholine from the vagus causes a decrease. A more complete explanation of the heart and its control can be found in physiology and medical texts.

THEORY

Since the heart is a dynamic system whose rate changes with stimuli and time, it lends itself very well to study by the analog computer. To put the results of the tests in a form suitable for analog computation required studies of available qualitative data. The steady-state heart rate as a function of the stimulus frequency was then expressed as follows:

$$HR = (HR_0 + Af_1)/(1 + Bf_2) \text{ beats per minute} \quad (1)$$

where

HR = heart rate
HR_0 = heart rate with no stimulus applied
f_1 = frequency of sympathetic stimulus, cps
f_2 = frequency of vagal stimulus, cps
A = experimentally determined coefficient relating steady-state heart rate to stimulus frequency f_1
B = similar coefficient relating heart rate to f_2

Here again, since the system is nonlinear, we see advantages of analog computer techniques.

EXPERIMENTAL METHODS

The experiments performed in preparation of this article were all conducted with the use of facilities of the Cardio-Vascular Laboratory at the Latter Day Saints Hospital, Salt Lake City, Utah.

In tests conducted, mongrel dogs were anesthetized with nembutal. After the nembutal had taken effect, the dogs were placed on the operating table and various test transducers were attached. Arterial blood pressure was recorded from the aortic arch just outside the left ventricle by means of a pressure

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gauge. This pressure in an electrical form was recorded on one channel of a multichannel tape recorder. The variation in blood pressure is very important because the heart rate can be determined from the pressure pulse of each heartbeat.

The electrocardiogram, or EKG, represents a graph of the depolarization or changing potential of the heart each time it beats. The EKG can be used to determine heart rate, but was used in the experiments conducted to detect heart "blocks" caused by stimulating the left vagus, as mentioned.

Since the vagus and sympathetic nerves act as primary control links to the heart, if all four nerves are severed this will essentially isolate the control of the heart so that external stimulation of these nerves will simulate control signals from the brain.

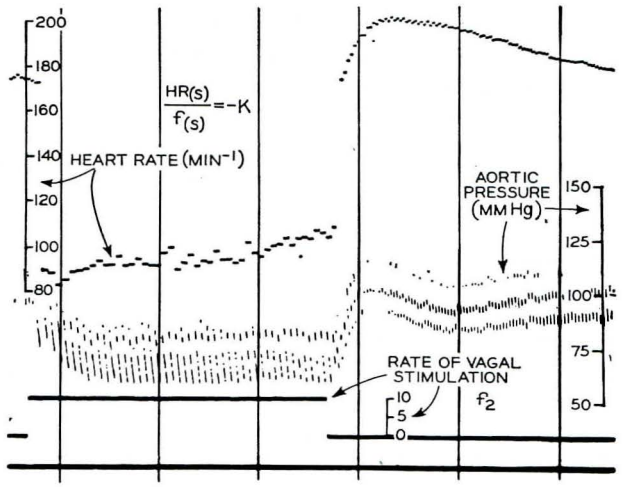

Fig. 1. Effect of stimulation of right vagus nerve on heart rate and arterial pressure

The nerve to be stimulated was placed across two platinum–irridium electrodes which were connected to a stimulator through an isolation transformer. The effect on heart rate resulting from stimulus of the vagus or sympathetic nerves depends not only upon the frequency of stimulus, but also upon the magnitude and duration of each stimulus pulse. These variables were easily controlled. However, the problem of electrode placement was more difficult to control and made quantitative comparison of response to stimulation of any two nerves difficult. Upon application of the stimulus an analog voltage, f_1 or f_2, proportional to the frequency of stimulation, was recorded on the tape to provide an analog "stimulus" which was later used for data reduction and simulation.

The multichannel FM magnetic tape recorder is an extremely valuable tool for medical research; besides providing storage for valuable data, the tape recorder allows the investigator to concentrate on the task of recording the basic data. Then, at some later time, the desired results can be computed from the tape.

Following each experiment the data obtained were recorded, by means of a mechanical oscillogram, on a photographic tape which allowed the experimenters to study the experiment and compute results. A typical section of recording film is shown in Fig. 1, with each of the traces appropriately labeled. The vertical lines are 10-second time markers.

The heart-rate indicator shown in Fig. 1 was obtained by programming the analog computer to produce a voltage proportional to the interval between pressure pulses; then, taking the reciprocal of this voltage, an output voltage proportional to the heart rate, but delayed by one beat, was obtained. By calibration of this voltage, the heart rate at any time could be determined by use of a scale, as shown in Fig. 1.

RESULTS

Determination of Steady-State Coefficients

Using the heart rate equation stated earlier (equation 1), the steady-state coefficients can easily be determined experimentally.

$$A = (HR_1 - HR_0)/f_1 \quad (2)$$

$$B = (HR_0 - HR_2)/HR_2 f_2 \quad (3)$$

where

HR_0 = heart rate with no stimulus applied
HR_1 = heart rate with only sympathetic stimulus
HR_2 = heart rate with only vagal stimulus
f_1, f_2 = frequency of stimulation of sympathetic and vagus, respectively

This information was easily obtained from records similar to Fig. 1.

Fig. 2 shows typical plots of A and B vs. f_1 and f_2, respectively. Note that as the frequency of stimulus f_1 to the sympathetic nerve is increased, the coefficient A becomes smaller at about the same rate that f_1 increases. Here, a condition for maximum heart rate is represented. Thus we see, as in many electric systems, that a saturation condition exists.

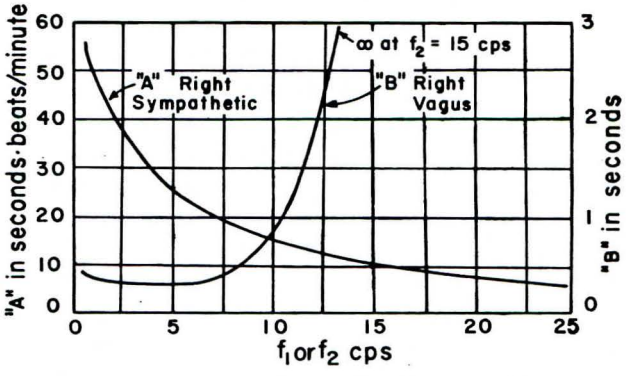

Fig. 2. Steady-state coefficients as a function of frequency

As may be noted from the plot for B, it goes to

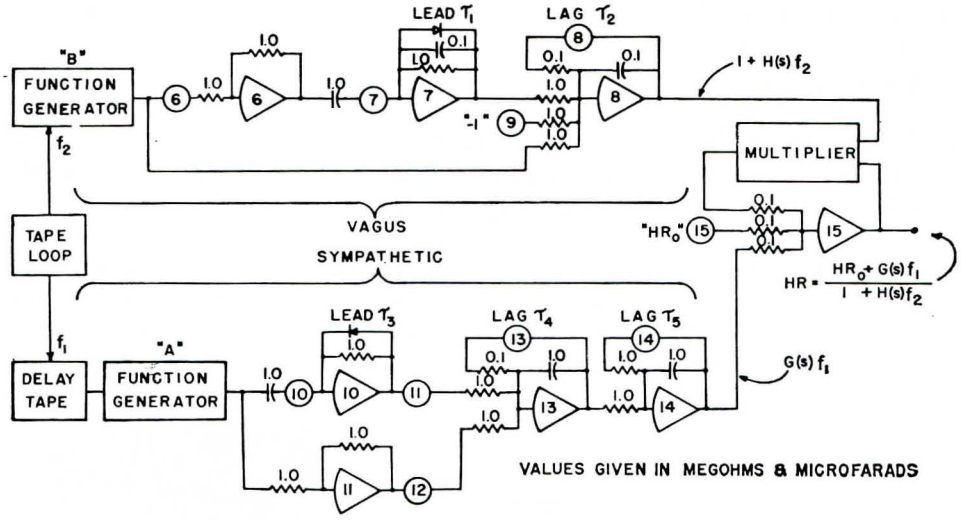

Fig. 3 Analog computer diagram

infinity at $f_2 = 15$ cps. This is a condition of cardiac arrest or of the heart stopping its action.

No systematic differences in the response to stimulation between right and left vagus and between right and left sympathetic nerves were observed. Exact comparison of absolute amplitude of response to stimulation of two nerves is made difficult by the fact that any variation in the electrode placement may result in variations in the number of fibers stimulated. However, in general it appears that stimulation of the right and left nerve (vagus or sympathetic) at 1 cps produces essentially the same response as stimulating either the right or left nerve at 2 cps. For this reason, it appears justifiable to treat the right and left nerves as part of a single system as far as their effect on the heart rate is concerned.

Dynamic Simulation

All analysis and discussion thus far have been on steady-state response of the heart. In order to provide a more complete quantitative analysis, it is necessary to make a study of the system's dynamic responses.

Since the coefficients A and B are dependent upon frequency variation of f_1 and f_2, respectively, it is convenient to work in the frequency domain instead of the time domain and express equation 4 in Laplace transform notation. Therefore

$$\mathrm{HR}(s) = [\mathrm{HR}_0 + G(s)f_1]/[1 + H(s)f_2] \qquad (4)$$

Vagus

The equation for the heart rate with only vagal stimulation is

$$\mathrm{HR}_2 = \mathrm{HR}_0/[1 + H(s)f_2] \qquad (5)$$

where it was found experimentally that $H(s)$ could be expressed in equation form as

$$H(s) = B(1 + \tau_1 s)^*/(1 + \tau_2 s) \qquad (6)$$

where B is the steady-state coefficient (Fig. 2), τ_1 and τ_2 are time constants, and s is the Laplace operator.

The "lead" term $(1 + \tau_1 s)^*$ is marked with an asterisk to indicate that it is present only when frequency f_2 is increasing; i.e., when the stimulus f_2 is turned on. The term $(1 + \tau_2 s)$ represents a "lag," and in this equation it represents the exponential return of the heart rate to HR_0 after the stimulus was removed.

To find the time constant for vagal stimulation, a study was made of the photographic record to find a section of the record where a representative response was obtained. Then, when the desired section on the tape was located, pertinent information was rerecorded onto a continuous loop, providing a method of repeated observation of the information. For vagal simulation, the output of the heart rate meter and the analog voltage f_2, representing the stimulus frequency, were rerecorded on the loop. The analog computer was then programmed as shown in Fig. 3. The function generator provided the nonlinear coefficient B; the other sections are

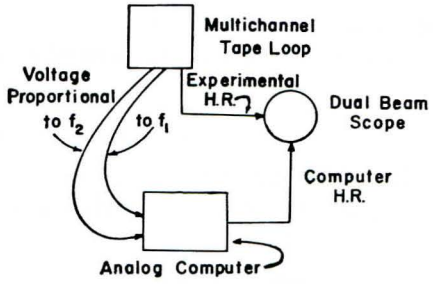

Fig. 4. Block diagram of simulating system

appropriately labeled. Since the lead term was to be present only on increasing f_2, it was necessary to include the diode as a feedback element of amplifier 7. For better simulation, and to expedite the procedure, the loop was played back at eight times normal speed.

Using the analog f_2 recorded on the loop for the "stimulus" of the analog computer, the heart rate as predicted by the computer was compared with the actual heart rate recorded on the loop; see Fig. 4. This was done with the use of a dual-beam oscilloscope and by the adjustment of appropriate potentiometers until the changes in the two heart rates were identical. The results of a typical simulation are shown in Fig. 6 with some typical time constant values given.

The "front edge" response to f_2 varied considerably even on the same dog. Several ideas were

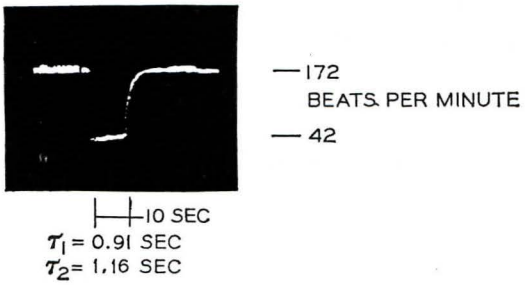

Fig. 5. Results of a typical vagal simulation

tested but none seemed to provide a suitable answer. Therefore, it must be concluded that this error was due to experimental method or more likely the action of some unknown mechanism.

Sympathetic

The equation for heart rate with sympathetic stimulation is

$$HR_1 = HR_0 + G(s)f_1 \qquad (7)$$

From experimental data it was found that no change in heart rate occurred for about 1.5 seconds after application of the stimulus. Then with a rather slow rise the heart rate approached a new value, where it remained until the stimulus was removed. Upon discontinuing sympathetic stimulation, the heart rate decreased slowly, requiring 20 to 30 seconds to return to the control heart rate HR_0.

Using a method similar to that employed for vagal simulation

$$G(s) = [A\epsilon^{-Ts}(1+\tau_3 s)^*]/(1+\tau_4 s)(1+\tau_5 s) \qquad (8)$$

where T is a fixed time delay of about 1.5 seconds, τ_3, τ_4, and τ_5 are time constants and A is the steady-state gain; see Fig. 2.

The methods used in simulating the sympathetic response are much the same as those used for vagal response. To provide the delay time, a delay tape was used. The "stimulus" $f_2\epsilon^{-Ts}$ was then applied to the computer. Other elements have functions similar to the vagus simulation. A typical stimulation is shown in Fig. 6 and representative time constants are $\tau_3 = 4.9$–19.6 seconds, $\tau_4 = 1.78$–2.7 seconds, $\tau_5 = 8.4$–27 seconds.

Nerve Interaction

If the reaction to vagal and sympathetic action followed as equation 4 predicts, then the two actions would be independent of each other. At the outset, they were thought to be independent; however, after careful experimentation it was found that such was not the case. From the data it appears that the vagal (slowing) response is dominant over sympathetic response. Thus, if the vagus and sympathetic are stimulated simultaneously with the same effective stimulus, the heart will slow down, following the "command" of the vagus nerve. This interaction is

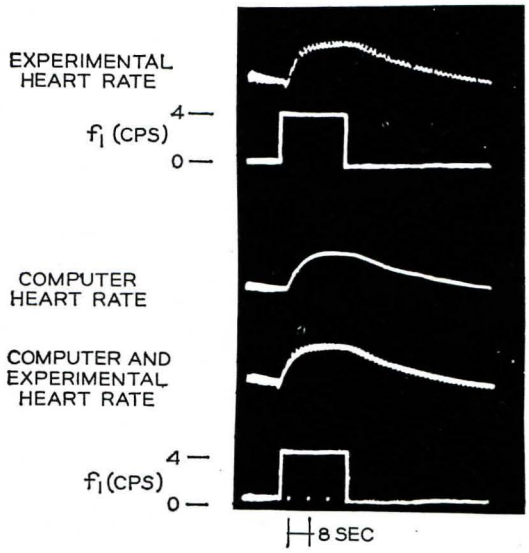

Fig. 6. Results of a typical sympathetic simulation

presently being studied in detail and it appears that soon a satisfactory solution will be made.

CONCLUSIONS

The goal of the project described in this article was to obtain a transfer function for the sinuauricular node of the heart, having both vagal and sympathetic stimulation as the inputs and the heart rate as the output.

The goal was not completely attained, however, because of the presence of vagal and sympathetic interaction. The reasons for the test were purely academic; it was hoped that the equations found might serve to give some insight into the basic biological processes (chemical reactions, diffusion, etc.) of the SA node.

This article deals with but one link of the heart control system. The performance of the complete system is influenced by the transfer functions of each of the system's components. As in the case of any closed-loop system, performance can be determined only by simultaneous solution of all the system's equations. The ultimate goal, therefore, is to obtain transfer functions for each of the system's components.